

REMARKS / ARGUMENTS

In response to the final Office Action of April 20, 2007, Applicant respectfully requests reconsideration and withdrawal of the final rejection of claims based on the remarks set forth below.

Claims 17 and 18 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claim 17 recites in relevant part: "wherein said nonionic surfactant is an amphiphilic substance whose hydrophilic component consists of polyethylene oxide and wherein said carrier composition is devoid of a hydrophilic phase." The position of the Examiner is that since the surfactant is part of the carrier, it is not clear how the surfactant which has a hydrophilic component does not contribute hydrophilic phase. See Office Action, page 3, item 4.

In response to the rejection, Applicant respectfully submits that one skilled in the art at the time the invention was made, would have understood an non-ionic, amphiphilic surfactant to have a distinct polar (hydrophilic) and non-polar (hydrophobic) region. Such a surfactant, although having a hydrophilic *region* within the substance, does not necessarily have to contribute to a hydrophilic *phase* within a pharmaceutical composition and certainly does not contribute to any hydrophilic phase in the carrier of the pharmaceutical composition as presently claimed.

A surfactant by definition lowers the interfacial tension between oil and water phases and is adsorbed at the interface of two surfaces e.g. of two immiscible liquids such as e.g. an aqueous liquid and a lipophilic liquid). See e.g., <http://pharmacy.wilkes.edu/kibbeweb/lab7.html> and http://en.wikipedia.org/wiki/Hydrophilic-lipophilic_balance, annexed hereto as Exhibit A and B respectively.

It is respectfully submitted that one skilled in the art at the time the application was first filed, would have understood that surfactants are classified as cationic, anionic and nonionic based on the type of polar group on the surfactant. Cationic surfactants

are often used as antibacterial agents because of their ability to disrupt the cell membrane of the microorganism. The ionized surfactants have a relatively high water solubility and thus generally make oil in water emulsions. A nonionic surfactant, as recited in claims 17 and 18, however, may be used to make either type of emulsion. See Exhibit A.

To assist formulators in the selection of an appropriate surfactant, the HLB score was developed. HLB stands for hydrophile-lipophile balance. Surfactants with a low HLB are more lipid loving and thus tend to make a water in oil emulsion while those with a high HLB are more hydrophilic and tend to make an oil in water emulsion. The HLB value of each surfactant is determined by an analysis of the characteristics of the surfactant. See Exhibit B.

The hydrophilic component of the presently claimed nonionic surfactant is "water loving" and therefore soluble in water, *including the aqueous environment of the gastrointestinal tract*. See specification, page 1, paragraph 3. In a suspension with a hydrophilic and lipophilic liquid such as in the gastrointestinal tract, the presently claimed non-ionic surfactant of claims 17 and 18 will be located at the interface of the two phases and the hydrophilic portion of the presently claimed non-ionic, amphiphilic surfactant will be dissolved in the aqueous liquid.

The second paragraph of section 112 requires that the specification of a patent conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. 35 U.S.C. § 112 ¶ 2 (2000). To satisfy this requirement, the claim, read in light of the specification, must apprise those skilled in the art of the scope of the claims. *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 27 USPQ2d 1123 (Fed. Cir. 1993). The definiteness of the language employed must be analyzed not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Moreover, claims need not "be plain on their face in order to avoid condemnation for indefiniteness; rather, what [this court has] asked is that the claims be amenable to construction, *however difficult that task may be.*" *Exxon*

research & Eng'g Co., v. United States, 265 F.3d 1371, 60 USPQ2d 1272 (Fed. Cir. 2001) (emphasis added).

It is respectfully submitted that as discussed fully above, and as evidenced by Exhibits A and B submitted herewith, claims 17 and 18, when read in the light of the specification and the prior art, are amenable to construction and apprise one skilled in the art of their scope. Withdrawal of the rejection of claims 17 and 18 under 35 U.S.C. §112, second paragraph, is therefore warranted.

Claims 11-20 have been rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Al-Razzak et al. (WO 98/40051). Applicant respectfully traverses the rejection for the following reasons. The present application was originally filed as a U.S. national phase application (371 application) of PCT/EP 94/02248 on July 8, 1994, which date precedes September 17, 1998, the publication date of Al-Razzak et al. The Examiner has acknowledged Applicant's claim for priority in the Office Action of January 27, 2005. Since Al-Razzak et al. was not patented or described more than one year before July 8, 1994, the rejection of claims 11-20 under U.S.C. §102(b) as anticipated by Al-Razzak et al. is improper and should be withdrawn.

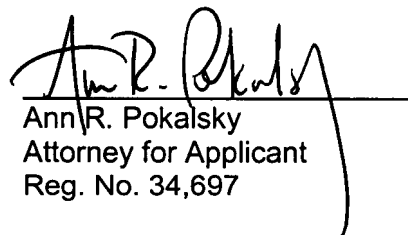
Likewise, since the present application has an international filing date of July 8, 1994, which date is prior to the international filing date of Al-Razzak et al. (March 12, 1998), the rejection of claims 11-20 under 35 U.S.C. §103(a) as obvious over Al-Razzak et al. is also improper and should be withdrawn.

In view of the foregoing remarks, it is respectfully submitted that the present application is in condition for allowance, which action is earnestly solicited.

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Laboratory 6 - Characteristics of Surfactants and Emulsions

A surface active agent (surfactant) possesses approximately an equal ration between the polar and nonpolar portions of each molecule. When placed in an oil-water system, the polar groups are attracted to or orient toward the water, and the nonpolar groups are oriented toward the oil. The surfactant molecule lowers the interfacial tension between the oil and water phases.

Realizing that the surfactant is adsorbed at the interface and by assuming that it is adsorbed in a nonmolecular layer, the amount of emulsifying agent required to emulsify a given volume of a liquid to a certain globular size can be calculated. The molecular weight and the cross-sectional area occupied by a molecule of the surfactant must be known.

Sodium Lauryl Sulfate has a molecular weight of 288 g/mole and a cross-sectional area of 22 square angstroms ($22 \times 10^{-16} \text{ cm}^2$). If 100 ml of oil is emulsified to an average globular diameter of 1 micron, the amount of sodium lauryl sulfate required can be calculated. The volume of a sphere is given by the equation:

$$V = 4/3 \text{ times } \pi \text{ times } r^3$$

The area of the same sphere can also be calculated using the equation:

$$A = 4 \text{ times } \pi \text{ times } r^2$$

Calculate the amount of Sodium Lauryl Sulfate needed. **This Calculation should be a part of your report**

Surfactants are classified as cationic (Zephiran), anionic (Aerosol OT) and nonionic (Tween) based on the type of polar group on the surfactant. Cationic surfactants are often used as antibacterial agents because of their ability to disrupt the cell membrane of the microorganism. The ionized surfactants have a relatively high water solubility and thus generally make oil in water emulsions. The nonionic surfactants, however, can be used to make either type of emulsion. To assist formulators in the selection of an appropriate surfactant, the HLB score was developed.

HLB stands for hydrophile-lipophile balance. Surfactants with a low HLB are more lipid loving and thus tend to make a water in oil emulsion while those with a high HLB are more hydrophilic and tend to make an oil in water emulsion. The HLB value of each surfactant is determined by an analysis of the characteristics of the surfactant. A list of HLB values for various surfactants is available in many references such as the Handbook of Pharmaceutical Excipients, 3rd Edition.

In the formation of a stable emulsion, it is advisable to have a blend of two or more nonionic surfactants rather than a single surfactant molecule. The HLB values of the surfactants are additive and the HLB value of the blend can be determined. For example, the HLB value of a 60% Tween 80 (HLB of 15) and 40 % Aracel 80 (HLB of 4.3) is

Arlacel 80	4.3 X 0.4 = 1.7
Tween 80	15.0 X 0.6 = <u>9.0</u>
	10.7

Some oils require different HLB surfactants to form the most stable emulsion. The required HLB value

for some of the most common oils used in pharmaceutical emulsions have been determined experimentally. Mixtures of these material will need a surfactant that matches the average HLB requirement of the oil components of the emulsion. For example, to form an o/w emulsion of stearyl alcohol you need a surfactant with an HLB value of 14 while to form an o/w emulsion of white petrolatum you need a surfactant with an HLB value of 10.5. If you wished to prepare an emulsion that contained an equal amount of the two substances, the HLB value of the surfactant used would be the average of the two or 12.25. You could use alligation to determine the amount of each of the two surfactants need to have a blend with the desired HLB.

Surfactant	HLB	Needed HLB	Parts Required
Arlacel 80	4.3		2.75
		12.25	
Tween 80	15		<u>7.95</u>
Total Parts			10.7

● **PROCEDURE.** There are three parts to this laboratory. One person should do part A , one person should do part B, and two people should work on part C. The surface orientation of molecules can be demonstrated by simple procedures. In fact, by employing careful technique, the area occupied by the surfactant may be measured with a minimum of equipment.

● **Part A.** Place approximately 5 g of pure stearic acid on the surface of hot water in a beaker. The fatty acid will melt to form a lens-shaped drop. Be sure it does not touch the sides of the beaker. You can use a glass rod to help keep the lens in the center of the beaker while it is cooling. Remove the heat and allow to cool. When it has solidified, remove it without disturbing the surfaces and allow it to dry.

With a few drops of water attempt to wet the bottom of the cake which solidified in contact with water. Record your observations. Add a few drops of water to the top of the cake which solidified in contact with the air and attempt to wet the surface. Record your observations.

● **Part B.** Using equal volumes of heavy mineral oil and distilled water, prepare 100 ml of an o/w emulsion using a blend of nonionic surfactants (Spans & Tweens). The average HLB required to make an oil in water emulsion of mineral oil is 12. Record the proportions and amounts of each surfactant you used. There is a list of the HLB values for a number of nonionic surfactants in the laboratory and on reserve in the PIC for your use. The total weight of the surfactant blend should be 10% w/w of the final mixture.

Now using the same surfactants but in different combination make a water in oil emulsion. The HLB needed to make a water in oil emulsion with mineral oil is 5. Record you observations about the quality of the emulsion and its overall appearance. Determine if you indeed made the desired emulsion type using the drop dilution or dye method.

While the HLB system allows us to calculate the appropriate ratio of surfactants to get a specific result the amount of surfactant blend can only be determined through trial and error.

- Part C. By various procedures given, prepare emulsions using the formula

Mineral Oil	35 ml
Sorbitan Monooleate HLB 4.3	2.5 ml
Purified water	12.5 ml

1. Place the oil and the emulsifier into a mortar. While triturating with a pestle, add the water. Now expose the emulsion to the hand homogenizer for 2 minutes. Determine the type of emulsion formed. Set aside to compare to the other emulsions.
2. Without prior mixing add all ingredients and use the hand homogenizer for two minutes. Determine the type of emulsion and set aside to compare to the other emulsions.
3. Place the oil and emulsifier in a Waring blender. With the blender operating gradually add the water. Determine the type of the emulsion formed and set aside to compare to the other emulsions.
4. Place the oil, emulsifier and water into the Waring blender. Turn the blender on for 30 seconds. Determine the type of the emulsion formed and set aside to compare to the other emulsions.
5. Decrease the concentration of oil to 25 ml and increase the amount of water to 22.5 ml. Make an emulsion by one of the four methods previously described. Determine the type of the emulsion formed and set aside to compare to the other emulsions.

Now examine all five emulsions and record your observations.
Did the mixtures make the type of emulsion you expected?

Hydrophilic-lipophilic balance

From Wikipedia, the free encyclopedia

The Hydrophilic-lipophilic balance of a surfactant is a measure of the degree to which it is hydrophilic or lipophilic, determined by calculating values for the different regions of the molecule, as described by Griffin in 1949^[1] and 1954.^[2] Other methods have been suggested, notably in 1957 by Davies^[3].

Griffin's method

Griffin's method for non-ionic surfactants as described in 1954 works as follows:

$$HLB = 20 * Mh / M$$

where Mh is the molecular mass of the hydrophilic portion of the Molecule, and M is the molecular mass of the whole molecule, giving a result on an arbitrary scale of 0 to 20. An HLB value of 0 corresponds to a completely hydrophobic molecule, and a value of 20 would correspond to a molecule made up completely of hydrophilic components.

The HLB value can be used to predict the surfactant properties of a molecule:

- A value from 3 to 6 indicates a W/O emulsifier
- A value from 7 to 9 indicates a wetting agent
- A value from 8 to 12 indicates an O/W emulsifier
- A value from 12 to 15 is typical of detergents
- A value of 15 to 20 indicates a solubiliser or hydrotrope.

Davies' method

In 1957, Davies suggested a method based on calculating a value based on the chemical groups of the molecule. The advantage of this method is that it takes into account the effect of strongly and less strongly hydrophilic groups. The method works as follows:

$$HLB = 7 + m * Hh + n * Hl$$

with:

m - number of hydrophilic groups in the molecule

Hh - Value of the hydrophilic groups

n - Number of lipophilic groups in the molecule

Hl - Value of the lipophilic groups

References

1. ^ Griffin WC: "Classification of Surface-Active Agents by 'HLB,'" Journal of the Society of

Cosmetic Chemists 1 (1949): 311.

2. ^ Griffin WC: "Calculation of HLB Values of Non-Ionic Surfactants," Journal of the Society of Cosmetic Chemists 5 (1954): 259
3. ^ Davies JT: "A quantitative kinetic theory of emulsion type, I. Physical chemistry of the emulsifying agent," Gas/Liquid and Liquid/Liquid Interface. Proceedings of the International Congress of Surface Activity (1957): 426-438

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Category: Surfactants

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